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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
07/27/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/642,284	KUMAGAI ET AL.	
	Examiner	Art Unit	
	Anne L. Holleran	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-32* is/are pending in the application.

4a) Of the above claim(s) *14-22 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13, 23-26 and 28-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed 5/7/2007 is acknowledged. Claims 1-12 were cancelled. Claims 28-32 were added.

Claims 13-32 are pending. Claims 14-22, and 27,drawn to non-elected inventions, are withdrawn from consideration. Claims 13, 23-26 and 28-32 (to the extent claims 23-26 comprise polypeptide products) are examined on the merits.

Priority

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on Jan. 17, 2003. It is noted, however, that applicant has not filed a certified copy of the 2003-038643 Japanese application.

Claim Rejections Withdrawn:

3. The rejections of claims 9 and 10 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment canceling the claims.

4. The rejection of claims 1, 2, 3, 5-8, 13, and 23-26 under 35 U.S.C. 102(b) as being anticipated by Deo (US 5,922,845; issued July 13, 1999) is withdrawn in view of the amendments to the claims.

5. The rejection of claims 24-26 under 35 U.S.C. 102(b) as being anticipated by Kipriyanov (Kipriyanov, G. et al., Protein Engineering, 10(4): 445-453, 1997) is withdrawn in view of the amendments to the claims.

6. The rejection of claims 1, 3-8, 12 and 23-26 under 35 U.S.C. 102(b) as being anticipated by Carter (US 6,407,213; issued June. 18, 2002) is withdrawn in view of the amendments to the claims.

7. The rejection of claims 1-6 and 23-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Negri (Negri, D.R.M. et al. British Journal of Cancer, 72: 928-933, 1995; cited in the IDS) is withdrawn in view of the amendments to the claims.

8. The rejection of claim 13 under 35 U.S.C. 102(b) as being anticipated by Clackson (Clackson, T. et al. Nature, 352: 624-628, 1991) is withdrawn in view of the amendments to the claims.

9. The rejection of claims 1-13 and 23-26 under 35 U.S.C. 102(a) as being anticipated by either Abstract #2125 (Abstract #3P-214, 61st Annual Meeting of the Japanese Cancer Association, August 20, 2002; cited in the IDS) or Abstract #3P-214 (Abstract #2125, 75th Annual Congress of The Japanese Biochemical Society, 74(8): August 25, 2002; cited in the IDS) is withdrawn in view of the amendment to the claims and upon further consideration of the English language summary of the references. Although antibodies with the same names are

taught in the abstracts, there does not appear to be a teaching of the structures of the claims products. Therefore, the abstracts do not appear to provide an enabling disclosure for how to make the claimed products.

Claim Rejections Maintained and New Grounds of Rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 13, 23-26 and 28-32 are/remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is indefinite because of the phrase "comprising an amino acid sequence". Because of the use of "an" instead of "the", one possible interpretation of the claims is that the variable regions recited in claim 13 have in common as little as a two amino acid sequence with any of the identified sequences (SEQ ID NO: 43, 44, 45 and 46).

Claim 13 is further indefinite because it is drawn to a single-chain polypeptide from a humanized diabody-type bispecific antibody comprising:". It is not clear is the single chain comprises the sequences set forth in sections "(A)" through "(E)" or if the diabody-type bispecific antibody comprises the sequences in set forth in sections "(A)" through "(E)". If it is the latter, then it is not clear what the structure is of the claimed "single-chain polypeptide from a humanized diabody-type bispecific antibody".

Claim 13 is further indefinite because it is drawn to a single-chain polypeptide from a humanized diabody-type bispecific antibody comprising "(A)" *or* "(B)", "(C)" , "(D)" *and* "(E)" [emphasis added]. Does applicant intend "(A)" ,"(B)", "(C)" , "(D)" *or* "(E)"?

Claim 13 is further indefinite because it appears to be drawn to single-chain polypeptides that will not have binding activity because, for example "(A)" is made up of the heavy chain from the OKT3 antibody and the light chain from the 528 antibody. The OKT3 antibody binds CD3, whereas the 528 antibody binds EGFR. It is not taught in the specification that pairing a heavy chain from the OKT3 antibody with the light chain of the 528 antibody will result in a single chain that will have binding function.

Claim 13 is further indefinite because it recites a heavy chain comprising a variable region comprising an amino acid sequence according to SEQ ID NO: 44, which is taught by the specification to be a light chain variable region; and it recites a light chain comprising a variable region comprising an amino acid sequence according to SEQ ID NO: 45, which is taught by the specification to be a heavy chain.

Claim 24 is indefinite because of the phrase "the diabody-type specific antibody according to claim 28". Claim 28 is drawn to a diabody-type bispecific antibody. Thus, "the diabody-type antibody" lacks antecedent basis.

Claim 26 is unclear because it recites a "humanized diabody-type bispecific antibody" of claim 28. Claim 28 refers to sequences that are found in figures 21 and 22, which the specification teaches are humanized sequences. Therefore, it is not clear why the phrase "humanized" is required.

Claims 28-32 are indefinite because they refer to the heavy chain of SEQ ID NO: 44, which is taught by the specification to be a light chain, and the light chain of SEQ ID NO: 45, which is taught by the specification to be a heavy chain.

Claim 28 is indefinite because of the phrase "consisting of two single-chain polypeptides selected from the group of (A)-(D)", which implies that each of "(A)" through "(D)" is a single-chain polypeptide, when it appears that each of "(A)" through "(D)" appears to recite the entire diabody-type bispecific antibody. This rejection would be overcome by amending the claim so that it is drawn to "A humanized diabody-type bispecific antibody, which consists of two single-chain polypeptides, selected from the group of consisting of..."

Claim 28 is further indefinite because of the phrase "comprising an amino acid sequence". Because of the use of "an" instead of "the", one possible interpretation of the claims is that the variable regions recited in claim 28 have in common as little as a two amino acid sequence with any of the identified sequences (SEQ ID NO: 43, 44, 45 and 46).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 13, 23-26 and 28-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for humanized diabody-type bispecific antibodies that

comprise all six CDRs of the two parent antibodies, or for single chain antibodies that comprise all six CDRs from a parent antibody, does not reasonably provide enablement for the single chain antibodies that are recited in claim 13. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Claim 13 is drawn to a single-chain polypeptide from a humanized diabody-type bispecific antibody. Claim 23 is drawn to a pharmaceutical composition comprising the antibody of claim 13. Claim 28 is drawn to diabody-type bispecific antibodies. As noted above or claim 13, it is not clear if the sequences recited in sections "(A)" through "(E)" are comprised within the structure of the humanized diabody-type bispecific antibody, or if they are the structures of the claimed single chain polypeptides. If sections "(A)" through "(E)" are the structures of the single chain polypeptides it is not clear how one of skill in the art would be able to use these structures, because, for example, the structure of "(A)" comprises a heavy chain variable region of an OKT3 antibody, which binds CD3, and the light chain variable region of a 528 antibody, which binds EGFR. Furthermore, as noted above for either claim 13 or 28, the claims recite "an amino acid sequence". Thus, the scope of the claims is much broader than if the claims recited

"the amino acid sequence" of SEQ ID NO: 43, 44, 45 and 46, because the use of "an amino acid sequence" means that the structures of the recited single chain polypeptides may contain only a 2 amino acid sequence in common with the reference sequence identifiers.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which heavy and light chain variable regions consists of three CDRs that provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity that is characteristic of a given antibody. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences, which maintain the required conformation of the CDRs, are required in order to produce a protein having antigen-binding function; and further, that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light chain variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff (Proc. Natl. Acad. Sci. USA, 79: 1979, 1982). Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that the single-chain polypeptides as defined by the claims, which may contain less that the full complement of CDRs from the heavy and light chain variable regions of the parent antibodies that bind CD3 and EGFR will have the required binding function of binding to either antigen.

The specification provides no direction or guidance regarding how to use the single chain polypeptides or diabody-type bispecific antibodies as defined by the claims, because the specification fails to teach how to make binding sites within single-chain polypeptides that do not contain all of the CDRs present in the parent antibodies. The relationship between structure and function in the protein and antibody arts is highly unpredictable. Therefore, one of skill in the art would have to engage in undue experimentation to practice the full scope of the claimed inventions. This experimentation would be undue experimentation because there is no guidance provided in the specification or in the prior art for producing useful antibodies that lack the full complement of CDRs from the parent antibody, and that also bind to either CD3 or EGFR with sufficient affinity to be useful as a pharmaceutical agent.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 13 and 23 remain rejected under 35 U.S.C. 102(b) as being anticipated by Kipriyanov (Kipriyanov, G. et al., Protein Engineering, 10(4): 445-453, 1997).

In light of the fact that claim 13 recites "comprising an amino acid sequence", and claim 13 is drawn to a single chain polypeptide, the rejection is maintained because Kiprianov teaches

a single chain polypeptide comprising a heavy chain and a light chain form the OKT3 antibody. Claim 23 is a pharmaceutical composition of claim 13, and pharmaceutical composition is interpreted as an intended use of a composition. Because the Kipriyanov single-chain antibody is from the OKT3 antibody it comprises an amino acid sequence from SEQ ID NO: 43 (for example "QV", amino acids 1 and 2 of SEQ ID NO: 43) (see Figure 2, page 448). It also happens to comprise an amino acid sequence from SEQ ID NO: 46 (for example "DI", amino acids 1 and 2 of SEQ ID NO: 46). Kiprianov teaches a composition of the scFv in PBS. Thus, Kiprianov teaches the claimed inventions.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne Holleran, whose telephone number is (571) 272-0833. The examiner can normally be reached on Monday through Friday from 9:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272-0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Official Fax number for Group 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Anne L. Holleran
Patent Examiner
July 21, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER